Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 2011;365:689-98.

Azithromycin for Prevention of COPD Exacerbations

Supplementary Appendix

Collaborators……2-3

Section A. Race/Ethnicity details…… 4

Section B. Effect of GOLD stage on the rate of AECOPDs and having to be hospitalized for AECOPDs…….. 5

Section C. St. George Respiratory Questionnaire…… 6

Section D. SF-36 scores……7-8

Section E. Inhaler use on enrollment at 12 months ……9

Section F. Effect of study drug on hearing ……..……10

Section G. Nasopharyngeal colonization and macrolide resistance…… 11

Section H. Serious adverse events and adverse events resulting in study drug discontinuation……12-13

Section I. Subgroup analyses..... 14-16

Collaborators

The COPD Clinical Research Network is supported by a Cooperative Agreement from the Division of Lung Diseases of the National Heart, Lung, and Blood Institute. At some sites General Clinical Research Centers (GCRC) were utilized; their M01 grants from the National Center for Research Resources are listed. Members of this Network, with their personnel and grant support are: **Brigham and Women's Hospital (Affiliated Sites: Fallon Clinic, West Roxbury Veterans Hospital)** – JJ Reilly, Jr, (PI), G R Washko (Co-PI), R Rosiello, M L Moy (Investigators), C Mayo, S Peterson, K Allain, A McDonald, B Kniskern, V Danilack K Matthess (Coordinators). Grant HL074428, GCRC Grant RR02635. **Denver Health Medical Center (Affiliated Sites: National Jewish Medical & Research Center, University of Colorado)** – RK Albert (PI), B Make (Co-PI), M Schwarz, C. Welch (Investigators), M Gilmartin, C Verano (Coordinators). Grant HL074409, GCRC Grant RR00051. **Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center** – R Casaburi, (PI), J Porszasz, (Investigator), RD Love, K Norulak, R Kiledjian, G Garcia (Coordinators). Grant HL074407, GCRC Grant RR00425. **Minnesota Veterans Research Institute, Minneapolis (Affiliated Sites: HealthPartners Research Foundation, Mayo Clinic)** – DE Niewoehner (PI), C McEvoy, KR Rice, PD Scanlon (Co-PIs), CB Bourassa, P Neuenfeldt, J Hart (Coordinators). Grant 1U10-HL074416. **Temple University** – GJ Criner (PI), N Marchetti, A. Satti, V Kim, J Mamary, F Cordova(Investigators), C Grabianowski, D Fehrle, H Criner, G Jones (Coordinators). Grant HL074408. . **University of Alabama at**

Birmingham – WC Bailey, JAD Cooper (Co-PIs), MT Dransfield, LB Gerald, P O'Reilly (Investigators), S Tidwell (Coordinator). Grant HL074418. **University of California, San Francisco** – SC Lazarus (PI), HA Boushey, PG Woodruff (Investigators), M Birch, R Sakurai, K Schardein, M Dyjak, Nguyen (Coordinators). 1U10-HL074431. **University of Maryland, Baltimore** – SM Scharf (PI), M Alattar, P Amelung, M Cowan, J Hanson, J Hasday, A Iacono, C Shanholtz, N Todd, A Verceles (Investigators), T Fitzgerald, Bell-Farrell W, Wood P (Coordinators). Grant HL074441, GCRC Grant RR16500. **University of Michigan, Ann Arbor** – FJ Martinez (PI), JL Curtis, MK Han, KR Flaherty, T. Standiford, SE Gay, TE Sisson (Investigators), D Thompson, L McCloskey, M Christensen, D White (Coordinators). Grant HL074422. **University of Pittsburgh** – F Sciurba (PI), J Bon (Investigator), L Kniolek, M Pitaro, R Folger (Coordinators). Grant HL074439, GCRC Grant RR00056. **University of Minnesota (Data Coordinating Center)** – JE Connett (PI), NR Anthonisen (Steering Committee Chair), C Wendt (Co-PI), M Skeans, W Patrek, H Voelker, S Harnden (Coordinators). Grant 1U10- HL074424. **Data and Safety Monitoring Board** – BB Bender, SF Kelsey, JR Landis, B Phillips, GM Turino, R Veatch, A Waldo, C Champlin, A Wanner. **Protocol Review Committee** – HW Kelly, J Maurer AJ McSweeny, RM Senior, EA Thom, PD Wagner, RL ZuWallack. **NHLBI** – G Weinmann (Deputy Director, Division of Lung Diseases), T Croxton (Director, Airway Biology & Disease Program), A Punturieri (Program Officer), MP Stylianou (Biostatistician).

Section A. Race/Ethnicity Details (N, %)

Race/Ethnicity	Azithromycin (N = 558)	Placebo (N = 559)
Other	19 (3)	22 (4)
Native American	2 (0.4)	2 (0.4)
Asian	6 (1)	4 (1)
Hispanic	11 (2)	14 (3)
Pacific Islander	0 (0)	2 (0.4)

Section B. **Effect of GOLD Stage on the Rate of AECOPDs and on Having to be Hospitalized for AECOPDs (mean ± SD).**

	Gold Stage		
	2	**3**	**4**
Azithromycin			
Patients (N)	148	222	186
Rate of AECOPD (/patient-year)	1.02 ± 0.15	1.53 ± 0.13	1.75 ± 0.17
Rate of AECOPDs requiring hospitalization (/patient-year)	0.50 ± 0.12	0.85 ± 0.12	0.74 ± 0.12
Control			
Patients (N)	148	226	180
Rate of AECOPD (/patient-year)	1.68 ± 0.16	1.75 ± 0.13	2.05 ± 0.28
Rate of AECOPDs requiring hospitalization (/patient-year)	0.65 ± 0.11	0.96 ± 0.12	1.03 ± 0.27

Section C. St. George Respiratory Questionnaire Scores

SGRQ Score*	Azithromycin		Placebo		P value
	N	Mean ± SD	N	Mean ± SD	
Enrollment	556	50.9 ± 16.4	555	50.1 ± 16.4	0.381
Six months	484	47.7 ± 16.3	483	48.1 ± 16.4	0.657
Twelve months	444	46.8 ± 16.7	453	48.0 ± 17.8	0.289
Δ enrollment - six months	484	-2.5 ± 11.6	483	-1.2 ± 10.5	0.076
Δ enrollment - twelve months	444	-2.8 ± 12.1	453	-0.6 ± 11.4	0.006

Individual SGRQ Scale Scores at Enrollment and 12 Months (mean ± SD)

	Azithromycin			Placebo			P value
SGRQ Scale*	Enrollment	12 M	Δ	Enrollment	12 M	Δ	
Symptoms	61.1 ± 19.7	54.1 ± 21.3	-7.0 ± 17.9	59.9 ± 19.7	56.2 ± 21.1	-3.7 ± 16.5	0.005
Impact	34.5 ± 18.0	32.4 ± 18.1	-2.1 ± 14.3	34.1 ± 18.2	34.1 ± 19.4	-0.0 ± 13.8	0.024
Activity	69.5 ± 19.0	67.9 ± 20.4	-1.6 ± 14.9	67.6 20.2	67.8 ± 21.6	+0.2 ± 14.3	0.076
Total	49.6 ± 15.7	46.8 ± 16.7	-2.8 ± 12.8	48.6 ± 16.5	48.0 ±17.8	-0.6 ± 11.4	0.005

* Minimal clinically important difference = -4 units

Section D. SF-36 Scores (* = P < 0.05, Azithromycin vs. Placebo)

	Start (Mean ± SD)	6 Months (Mean ± SD)	12 Months (Mean ± SD)
Azithromycin			
Vitality	47.1 ± 21.2	48.3 ± 21.1	46.9 ± 21.9
Physical functioning	36.5 ± 24.3	39.3 ± 25.8	38.4 ± 25.1
Bodily pain	68.3 ± 26.5	68.9 ± 26.2	68.7 ± 25.9
General health perceptions	40.1 ± 21.6	41.8 ± 20.9*	41.1 ± 20.8
Physical role functioning	36.5 ± 24.3	39.3 ± 25.8	38.4 ± 25.1*
Emotional role functioning	67.8 ± 40.5	66.5 ± 41.3	68.6 ± 41.5
Social role functioning	70.6 ± 26.0	71.7 ± 25.4	71.2 ± 26.5
Mental health	75.5 ± 18.2	75.9 ± 17.7	76.2 ± 18.1
Aggregate physical score	-1.82 ± 0.97	-1.69 ± 0.97	-1.73 ± 0.97
Aggregate mental score	0.25 ± 1.01	0.21 ± 1.02	0.26 ± 1.06
Placebo			
Vitality	47.9 ± 20.5	46.9 ± 20.8	48.6 ± 22.0
Physical functioning	37.5 ± 23.2	38.6 ± 24.1	38.4 ± 25.5
Bodily pain	69.2 ± 26.8	69.1 ± 26.0	69.4 ± 26.8
General health perceptions	39.7 ± 20.1	39.1 ± 20.3	39.5 ± 21.1
Physical role functioning	35.5 ± 39.3	41.4 ± 41.0	40.4 ± 41.4
Emotional role functioning	67.6 ± 41.5	68.3 ± 41.5	69.7 ± 40.1
Social role functioning	69.8 ± 27.3	70.8 ± 26.9	70.1 ± 26.7
Mental health	74.2 ± 18.4	75.2 ± 18.0	75.8 ± 18.4

Aggregate physical score	-1.75± 0.95	-1.70 ± 0.98	-1.72 ± 0.99
Aggregate mental score	0.19 ± 1.09	0.18 ± 1.02	0.23 ± 1.06

Section E. Inhaler Use on Enrollment and at 12 Months

	Enrollment (%)	12 Months (%)
Azithromycin		
Any ICS	74.7	76.0
Any LABA	75.6	76.9
Any LAMA	64.9	66.2
Placebo		
Any ICS	79.3	78.9
Any LABA	73.6	77.4
Any LAMA	62.9	64.8

All P > 0.10

Section F. Effect of Study Drug on Hearing

Interval	Group	N	Mean Δ db (SD)	95% CI	P Value
Enrollment to 3rd month	Azithromycin	512	-0.7 (4.1)	-1.0, -0.3	
	Placebo	513	-0.0 (4.2)	-0.4, 0.4	0.011
Enrollment to 12th month	Azithromycin	420	-1.2 (4.2)	-1.6, -0.8	
	Placebo	426	-0.9 (4./1)	-1.3, -0.5	0.25
3rd to 12th month	Azithromycin	411	-0.6 (4.2)	-1.0, -0.2	
	Placebo	417	-1.0 (4.3)	-1.4, -0.6	0.18

Section G. Nasopharyngeal Colonization and Macrolide Resistance

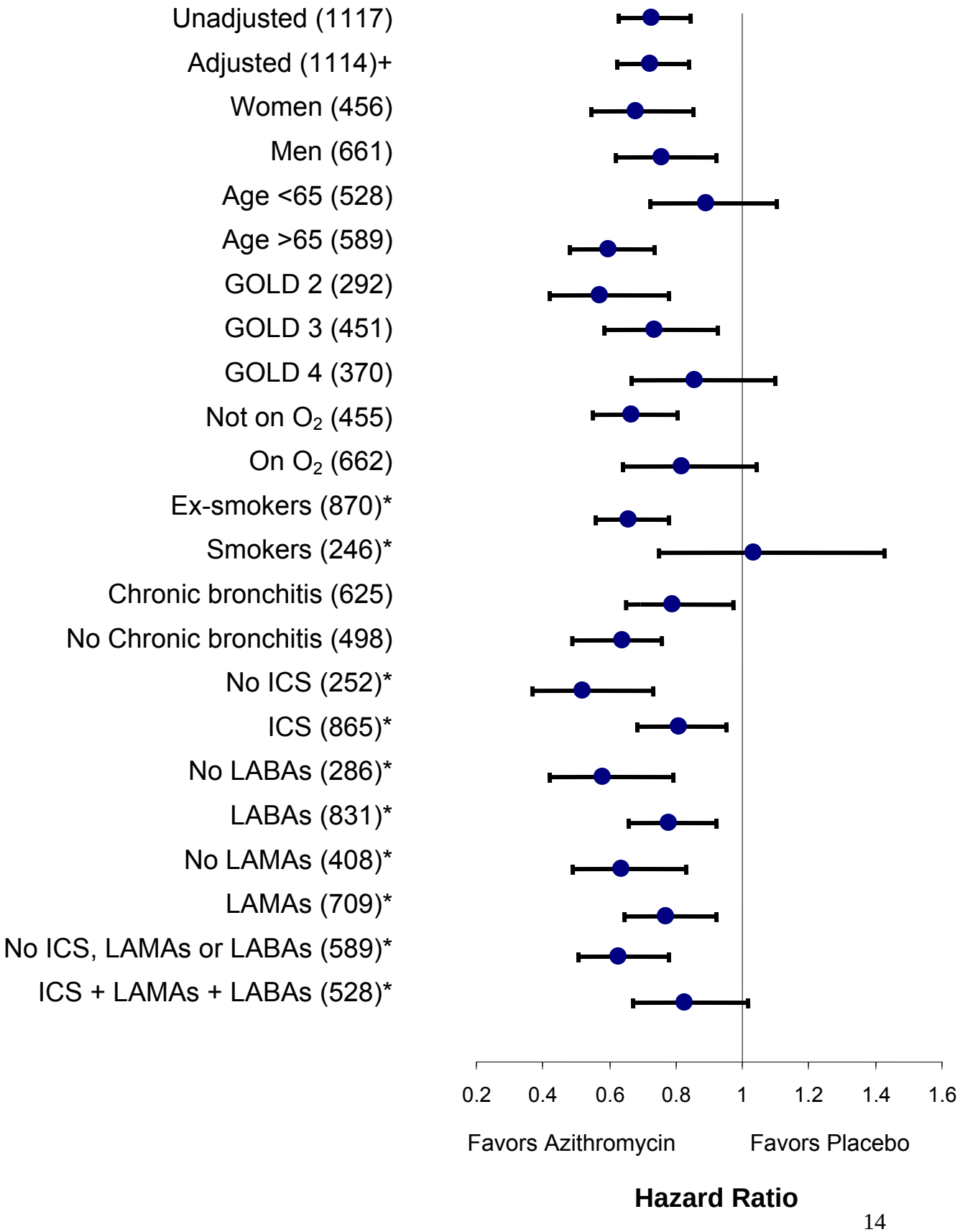
	Azithromycin		Placebo	
	Patients Colonized N (%)	**Macrolide Resistant N resistant/ N tested (%)**	**Patients Colonized (N, %)**	**Macrolide Resistant N resistant/ N tested (%)**
On enrollment				
S. aureus	60 (10.7)	16/35 (46)	71 (12.7)	23/37 (62)
S. pneumoniae	6 (1.1)	1/2 (50)	6 (1.1)	3/7 (43)
Hemophilus spp	0 (0)	3/4 (75)	0 (0)	2/3 (67)
Moraxella spp	13 (2.3)	3/3 (100)	6 (1.0)	0/2 (0)
Total	79 (14.1)	23/44 (52)	83 (14.8)	28/49 (57)
During course of study				
S. aureus	59 (10.6)	34/41 (83)	127 (22.7)	30/87 (34)
S. pneumoniae	6 (1.1)	2/2 (100)	15 (1.8)	2/4 (50)
Hemophilus spp.	1 (0.2)	2/3 (67)	3 (0.5)	5/7 (71)
Moraxella spp	0 (0)	0/1 (0)	27 (5.8)	7/10 (70)
Total	66 (11.9)	38/47 (81)	172 (30.8)	44/108 (41)

Section H. Serious Adverse Events and Adverse Events Resulting in Study Drug Discontinuation.

	Serious Adverse Events, N			Adverse Events Leading to Drug Discontinuation, N		
	Azithromycin	**Placebo**	**P value**	**Azithromycin**	**Placebo**	**P value**
Non-Fatal						
Pneumonia	26	41	0.11			
Neoplasm	6	8	0.62	0	3	0.25
GI tract	15	21	0.38	11	6	0.23
QTc prolongation	1	2	0.57	6	4	0.55
Other cardiovascular	29	33	0.68			
Other	107	107	0.97			
Total, Non-fatal	184	212	0.29			
Fatal (death prior to 12 M)						
COPD	10	7	0.48			
Cardiovascular	1	1	1.00			
Neoplasm	1	5	0.09			
Other	0	2	0.50			
Unknown	6	5	0.77			
Total, Fatal	18	20	0.87			
Hearing decrement				142	110	0.04
Tinnitus				4	4	1.00

Allergic reactions				5	8	0.58
Abnormal lab tests				4	3	0.73
Other				10	17	0.24
Total (adverse events leading to discontinuation)				182	155	0.14

Section I. Subgroup analyses (total number performed = 22)



The endpoint assessed in all subgroup analyses in the forest plot was time to first AECOPD. Interactions of the treatment with the factors defining the subgroups were assessed using interaction terms in Cox regressions. The specific interactions tested were:

Interaction	P value	Description
Azithromycin * age (< 65 vs ≥ 65)	P = 0.012	Older = more effect
Azithromycin * COPD Hospitalizations	P = 0.053	Hospitalization = less effect
Azithromycin * Gender	P = 0.550	
Azithromycin * Smoking at enrollment	P = 0.012	Smokers = less effect
Azithromycin * FEV1 (% pred)	P = 0.234	
Azithromycin* Gold Class	P = 0.164	
Azithromycin * Steroid use past year	P = 0.074	Steroid use = less effect
Azithromycin * ICS use at enrollment	P = 0.032	ICS use = less effect
Azithromycin * LABA use at enrollment	P = 0.201	
Azithromycin * LAMA use at enrollment	P = 0.299	

All subgroup analyses were prespecified. All had sample sizes that were much smaller than that of the total patient population. The confidence intervals shown in the Figure are not adjusted for multiple comparisons. Accordingly, the putative effects of treatment group in the subgroups indicated may represent false positives. Given that 19 analyses were carried out, if the null hypothesis was in fact true for each, and if the comparisons were all independent, there is a 62% chance that at least one of the 22 analyses would have yielded a result

significant at the 0.05 level. Accordingly, while some of these hazard ratios suggest potentially important differences in azithromycin effectiveness in various subgroups, we believe they do not provide sufficient rationale for guiding treatment in any of the subgroups without additional studies designed to assess these differences specifically.